# Calcineurin inhibitors in chronic urticaria

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**Purpose of review**
The purpose of the review is to review the pathophysiology, available data, and our current recommendations for calcineurin inhibitor (cyclosporine and tacrolimus) treatment in antihistamine refractory chronic idiopathic urticaria (CIU) patients.

**Recent findings**
Low-dose cyclosporine (<5 mg/kg per day) may have unique immunological modulating properties beyond mast cell and basophil stabilization in CIU. Starting CIU treatment with very low cyclosporine dosages (1 mg/kg per day) and titrating based on response and side-effects may decrease adverse events while preserving efficacy. In cyclosporine responsive patients failing cyclosporine taper, case series data support the safety and efficacy of long-term (5–10 years), very low dose (1–2 mg/kg per day) cyclosporine treatment with appropriate clinical monitoring.

**Summary**
For CIU patients refractory to antihistamines, low-dose cyclosporine therapy (<3 mg/kg per day) with appropriate laboratory monitoring provides an alternative with an acceptable side-effect profile. Long-term (>12 months) moderate-dose (2.5–5 mg/kg per day) cyclosporine treatment may cause longitudinal increases in serum creatinine. However, decreasing or stopping cyclosporine dosing reverses measured nephrotoxicity in the vast majority of patients, and some patients with careful monitoring can tolerate very low-dose cyclosporine (<2 mg/kg per day) for longer periods. Tacrolimus is an alternative to cyclosporine with a slightly different adverse effect profile. Minimal data are available on its use in chronic urticaria.

**Keywords**
calcineurin inhibitors, chronic idiopathic urticaria, chronic urticaria, cyclosporine, tacrolimus

## INTRODUCTION

The etiological enigma, significant morbidity, and commonplace antihistamine treatment failure complicate chronic urticaria management. With a lifetime prevalence of 1.8–2.9% and without an identifiable cause in 75–90% of cases, chronic idiopathic urticaria (CIU) affects a significant portion of the population and often provokes unnecessary dietary modifications and laboratory testing [1,2▪,3▪,4▪▪]. Chronic urticaria's unpredictable attacks, sleep disruption, and decreased work productivity decrease quality-of-life scores similar to patients awaiting a coronary artery bypass [3▪].

As a first-line therapy, second generation $H_1$-antihistamines at up to four times the standard dose provide only 38–55% of CIU patients symptom resolution, and sedation limits dosing in 10–15% of patients [3▪,5,6,7▪,8,9]. Antihistamine resistant CIU patients typically respond to corticosteroids; however, corticosteroid's long-term utility is limited by significant side-effects such as hyperglycemia, osteoporosis, weight gain, osteonecrosis, and glaucoma. Some guidelines suggest adding leukotriene receptor antagonist; however, efficacy evidence is considered low [10–12]. Dapsone, sulfasalazine, methotrexate, interferon, plasmapheresis, phototherapy, doxepin, cyclosporine A (CsA), tacrolimus, and omalizumab have all been proposed as next line treatment for $H_1$-antihistamines refractory CIU [10]. Other than a handful of randomized CsA studies and a few recent industry sponsored omalizumab trials, very few data exist to support most of these interventions. This article will review calcineurin inhibitors (cyclosporine A, tacrolimus) use in CIU management.

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## KEY POINTS

- Limited, but growing data support the efficacy and safety of low-dose cyclosporine for the treatment of antihistamine refractory chronic idiopathic urticarial (CIU).
- Low-dose cyclosporine (<3 mg/kg per day) adjusted to clinical response and side-effects may improve outcomes.
- Cyclosporine use requires careful clinical and laboratory monitoring for side-effects.
- Cyclosporine likely has numerous mechanisms by which CIU symptoms are reduced.
- Tacrolimus is an alternative calcineurin inhibitor therapy but has not been well studied in chronic urticaria.

## CALCINEURIN INHIBITORS' ROLE IN CHRONIC URTICARIA DISORDER

Effective CIU therapy derives from our understanding of this disorder. With skin biopsies resembling late-phase allergen-mediated reactions and the high affinity IgE receptor (FcεRI) autoantibodies in 40% of patients, immunological factors likely play a key role in CIU [13,14]. Specifically, mast cell and basophil IgE-receptor (FcεRI) activation and decreased peripheral FOXP3 positive, regulatory T cells (Tregs), represent two of many proposed CIU immunological mechanisms [15,16▪].

Calcineurin inhibitors' immunomodulation provides a therapeutic rationale for CIU treatment. In-vitro studies of mast cells and basophils pretreated with CsA or tacrolimus (FK-506) cause dose-dependent histamine release inhibition in non-CIU and CIU patients [17–21]. CsA treatment may also reduce histamine-releasing autoantibodies and reduced autologous serum skin test (ASST) response rates [22▪▪]. Cyclosporine-related Treg population increases, as in atopic dermatitis, provide yet another pharmacotherapy mechanism [16▪,23]. Nevertheless, the multiple faceted immunomodulation of calcineurin inhibitors and phenotypic variation of CIU cloud the precise therapeutic mechanism.

## CYCLOSPORINE: RANDOMIZED CONTROLLED AND PROSPECTIVE CLINICAL TRIALS

Very few, quality prospective studies have evaluated CsA treatment for CIU. A *PubMed* search limited to randomized controlled trials on 18 April 2012 using the text strings 'urticaria' and 'cyclosporine' with cultural spelling variations yielded only four results. Expanding the query limits to clinical trials yielded only 11 results. This data scarcity increases the weight of each study in evidenced based decision making.

### Study populations

Appropriately applying clinical trial results starts with understanding the study populations. All reviewed prospective trials studied adults with antihistamine refractory CIU [22▪▪,24▪▪,25–28,29▪▪,30,31]. However, the doses of antihistamines used to determine them to be 'antihistamine refractory' was often quite modest. As seen in Table 1 [22▪▪,24▪▪,25–28,29▪▪,30–32], other inclusion criteria differed including characteristics such as steroid dependence for symptom control or autoimmune CIU as assessed by positive ASST testing. Exclusion criteria varied broadly from only absolute CsA contraindications to extensive requirements such as other causes of urticaria, malignant diseases, use of potentially nephrotoxic drugs, hypertension, abnormalities in basic laboratory results, and seizure history. Exclusion criteria numerical totals listed in Table 1 imply relative restrictiveness. Finally, important study design features such as blinding, randomization, placebo control, measurement instruments, intention to treat analysis, and variances in intention to treat protocol have been noted when pertinent as a qualitative reference.

### Cyclosporine dosages

Differing cyclosporine length of treatment, dosage and taper complicate a direct comparisons and summation of study results. Most studies used 2.5–5 mg/kg per day. Treatment duration ranged from 4 to 20 weeks with long studies usually featuring cyclosporine tapers [22▪▪,24▪▪,25–28,29▪▪,30–32]. Very few of the studies used or reported serum cyclosporine levels.

### Cyclosporine results

Despite varying study protocols, nearly all of the studies reviewed reveal impressive response rates to cyclosporine treatment ranging from 40 to 100% (numerically weighted mean 71%) [22▪▪,24▪▪,25–28,29▪▪,30–32]. Studies with shorter cyclosporine treatment durations or aggressive tapers generally report lower response rates and higher relapse rates [22▪▪,27,29▪▪,30,32]. Of those patients responding to therapy, many studies reported significant remission induction (absence of chronic urticaria off cyclosporine) rates of 25–85% (numerically weighted mean 37%) [22▪▪,24▪▪,25–28,29▪▪,30–32].

**Table 1. Prospective studies of cyclosporine in chronic urticaria**

| Study | | | | Study population | | | | | Treatment | | | Results | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Design | Author | Year | Key study features | Group | *N* | % ASST | Exclusion criteria | Follow-up duration | Cyclosporine dosage (mg/kg per day) | Brand | Taper | Primary outcome | % Response at the end of treatment | %Complete remission | Relapse requiring steroids or CsA | % Side-effects | Drop out during treatment |
| Double-blind placebo controlled | Grattan *et al.* [22▪▪] | 2000 | Randomized, double blind placebo controlled: - no intention to treat; - cetirizine 20 mg/day continued in all | CsA for 4 weeks | 20 | 100 | 17 | 26 | 4 for 4 weeks | S | No | *At 4 weeks CsA treated patients improved more than high dose antihistamines*[a] | *40*[a] | *25*[a] | *75* | 97% | 5% |
| | | | | Initial placebo | 10 | 100 | | 26 | NA | P | NA | | 0 | 0 | | 50% | 0% |
| | | | Open CsA trial - from the nonresponder group | Nonresponders continuing CsA | 7 | 100 | | 26 | 4 for 8 weeks | S | No | Some patients will respond at 8 weeks of CsA therapy | 57 | | | 97% | 14% |
| | | | Open CsA trial- from the placebo group | Placebo converted to CsA | 10 | 100 | | 26 | 4 for 4 weeks | S | No | CsA for 4 weeks has some responders | 70 | | | | 0% |
| | Vena *et al.* [24▪▪] | 2006 | Randomized, double-blind placebo controlled trial: - cetirizine 10 mg/d continued in all patients | CsA for 16 weeks | 33 | | 5 | 24 | 5 for weeks 1–2; 4 for weeks 3–4; 3 for weeks 4–8; Placebo 8-16 | S; N | Yes | *CsA improved severity Score significantly improved at 8 weeks vs. placebo*[a] | 62 | | *42*[a] | *64%*[a] | 24% |
| | | | | CsA for 8 weeks | 31 | | | | 5 for weeks 1–2; 4 for weeks 3–4; 3 for weeks 4-16 | | Yes | | 53 | | 19 | *72%*[a] | 42% |
| | | | | Placebo | 35 | | | | 0 | P | NA | | 25 | | 31 | 46% | 49% |
| Open-label, case-controlled | Baskan *et al.* [25] | 2004 | OL Rand: -2 CsA durations | CsA for 12 weeks | 10 | 100 | 18 | 72 | 4 for weeks 1–2 | U | No | No response difference between CsA Groups | 80 | | 13 | 80% | |
| | | | | CsA for 4 weeks | 10 | 100 | | 0 | 4 for weeks 1–4 | U | No | | 50 | | 0 | 40% | |
| | Loria *et al.* [26] | 2001 | OL Rand control CsA: - control- prednisone 20 mg/day | CsA for 8 weeks | 10 | | 13 | 52 | 8 for weeks 1–8 | U | Yes | TSS decreased in both CsA and prednisone groups | 100 | 80 | | 20% | |
| | | | | Prednisone | 10 | | | | 0 | C | NA | | 100 | | | 30% | |
| | Serhat Inaloz *et al.* [27] | 2008 | Prospective, matched case-control, open trial | CsA for 4 weeks | 27 | 41 | 15 | 4 | 2.5 for weeks 1–4 | S | No | *Decreased UAS scores in all CIU patients on CsA*[a] | 100 | 70 | | 4% | 0% |
| | | | | Healthy controls | 24 | 0 | | | 0 | NA | NA | | NA | NA | | NA | 0% |
| | Toubi, E, *et al.* [28] | 1997 | OL Rand control: - controls 10; - no intention to treat | CsA for 12 weeks; - steroid dependent | 25 | 40 | | 26 | 3 for weeks 1–6; 2 for weeks 7-12 | U | Yes | Decreased CUS noted in all patients | 76 | 44 | 0 | 20% | 24% |
| | | | | Nonplacebo: -steroid dependent | 10 | 42 | | 26 | 0 | NA | NA | | 0 | 0 | NA | | 0 |

(*Continued*)

**Table 1 (*Continued*)**

| Study | | | | Study population | | | | Treatment | | | Results | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Design | Author | Year | Key study features | Group | N | % ASST | Exclusion criteria | Follow-up duration | Cyclosporine dosage (mg/kg per day) | Brand | Taper | Primary outcome | % Response at the end of treatment | %Complete remission | Relapse requiring steroids or CsA | % Side-effects | Drop out during treatment |
| Prospective open-label | Boubouka *et al.* [29▪▪] | 2011 | OL: - start 1.5–2.5 mg /kg; - monthly symptom based dosage adjustments | CsA for 20 weeks | 30 | 100 | 10 | 72 | 216 for weeks 1–4; 1.92 for weeks 5–8; 1.33 for weeks 9-12; 0.83 for weeks 13-16; 0.55 for weeks 17-20 | U | Yes | *Decrease in symptom scores in every month of CsA treatment except month 5*[a] | 88% | 77 | 13 | 40% | 23% |
| | Di Gioacchino *et al.* [30] | 2003 | RCT- converted to OL due to control failures | CsA for 16 weeks: - steroid dependent | 20 | 100 | 7 | 28 | 5 for weeks 1–8; 4 for weeks 8-16 | N | Yes | *Decreased CSS from baseline at end of 16 week*[a] | *95* | 40 | 5 | 18% | 10% |
| | Ohtsuka [31] | 2010 | OL, prospective | CsA for 16 weeks | 15 | 53 | 4 | 16 | 3 for week 1-12; Taper week 12-16 | N | Yes | Decreased CIU symptoms and CRPs | 100 | | | | 0% |
| | Iller *et al.* [32] | 1999 | OL without controls | CsA treatment | 15 | | | | 5 for week 1; 3.5 for week 2; 2.5 for week 3–7 | U | Yes | Week 1 All responded, week 2 33% relapse, week 3 80% relapse | 13 | 13 | 50 | | 87% |

Total follow-up duration in weeks. Empty cell = data not available from study. C, corticosteroid studies listed by strength of study design (highest to lowest); CIU, chronic idiopathic urticaria; CsA, cyclosporine A; OL, open-label study; P, placebo; Rand, randomized; RCT, randomized controlled trial; Treatment, cyclosporine (S, Sandimmune; N, Neoral; U, unknown).*
[a]Statistically significant in the study.

Of cyclosporine responsive patients, 5–75% (numerically weighted mean 13%) required steroids for relapse during the follow-up periods [22▪▪,24▪▪,25–28,29▪▪,30,31].

Most studies reported adverse events that occur in a dose-dependent manner. Reported adverse events ranged widely from 4 to 97% (numerical weighted average 47%) [22▪▪,24▪▪,26–28,29▪▪,30,31]. Observed adverse drug events included gastrointestinal complaints (diarrhea, abdominal pain), hirsutism, headache, tingling (lips, hand fingers), arthralgia, and gingival hyperplasia. In studies allowing decreased dosing for adverse events, most reported events improved on lower dosages [22▪▪,24▪▪,25–28,29▪▪,30,31]. High dropout rates, as noted in Table 1, confound the actual reported adverse events.

## CYCLOSPORINE-RETROSPECTIVE CHART REVIEWS AND CASE SERIES

Fradin *et al.* [33] reported one of the first successful CIU treatments with cyclosporine. Subsequently, numerous case studies and a few larger retrospective chart reviews have evaluated cyclosporine in CIU. Some of these studies provide unique clinical insight; however, known potential study design biases caveat the clinical strength of these observations.

### Very low dose cyclosporine

Retrospective chart review by Hollander *et al.*'s [34▪▪] reported over 100 patients with average 25-month CIU duration who underwent their center's typical CsA CIU treatment protocol. Starting with 1 mg/kg per day and increasing by 25–50 mg/day every 2–4 weeks, their protocol targets complete remission or a cyclosporine trough of 100–200 ng/ml. Clinical responders are tapered off CsA over the next 6 months, and at 1–2 months nonresponders are weaned off cyclosporine [34▪▪]. Interestingly, this low dose with upward titration strategy yields an impressive 78% remission rate with average dosages of 1.63 mg/kg per day [34▪▪]. Additionally, only 35% reported adverse medication events with 6% requiring discontinuation due to adverse events [34▪▪]. However, remission induction required 20.5 weeks on average, generally longer than the higher CsA dose studies, and the patients had shorter pretreatment CIU durations than other studies.

### Long-term usage of cyclosporine

Retrospective data on 120 patients, CIU cyclosporine treatment cohort by Kessel and Toubi [35▪▪] provided real-world insights on clinical efficacy and long-term consequences. When starting at

3 mg/kg per day, side-effects caused 17% of patients to discontinue treatment in the first 2 weeks. Of the patients tolerating 3 months of cyclosporine treatment, 62% experienced a highly beneficial outcome and in another 20% cyclosporine was considered beneficial [35▪▪]. Most uniquely, a small subset of 20 individuals were continued on very low cyclosporine dosing (1–2 mg/kg per day) for 5–10 years without significant adverse events, decreases in renal function, or malignancies [35▪▪]. These data support the safety and efficacy of long-term low-dose cyclosporine; however, future prospective studies with a larger number of participants are needed to confirm this hypothesis.

### Effect of cyclosporine dosage on response

Retrospective cohort trial of 110 steroid-dependent CIU patients of Di Leo *et al.* [36] evaluated outcomes as stratified by three different low-dosage treatment dosage groups (A, 1–1.5 mg/kg per day; B, 1.6–2 mg/kg per day; and C, 2.1–3 mg/kg per day). Each patient's respective age, preexisting hypertension, and dysmetabolism were considered nonsystematically to determine individual starting dosages [36]. Inverse correlations were noted between daily CsA dosage and total symptom severity score 2 months after discontinuing treatment (A, 63%; B, 76%; and C, 85%) and complete symptom resolution (A, 28%; B, 37%; and C, 45%) [36]. However, significant side-effects, such as reversible creatinine increases, directly correlated with increased CsA dosages [36]. The relapse rate following treatment was noted to be 11% with 87% of those responding to retreatment with CsA [36]. Finally, the mean serum cyclosporine level of $65.4 \pm 10.8$ ng/ml supports the efficacy of lower target serum levels [36].

### Cyclosporine usage in pediatrics

The only CsA for CIU data available in the pediatric population is a small retrospective review article [37]. Seven patients received 3 mg of cyclosporine divided into twice-daily dosages with target peak cyclosporine levels less than 200 ng/ml [37]. Treatment duration ranged from 10 weeks to 7 months with clinical improvement noted in all patients [37]. CIU relapse was noted in four of seven patients. The encouraging results of this small case series provide limited evidence-based guidance in children with chronic urticaria.

## CYCLOSPORINE: SAFETY

Cyclosporine dosages of more than 5 mg/kg per day may have complications of malignancy, infection, hypertension, and nephrotoxicity; however, low-dose cyclosporine (<5 mg/kg per day), as used in chronic urticaria and dermatological conditions, may have a lower side-effect profile as detailed in Table 2. A large ($n = 1252$), open, prospective, low-dose cyclosporine (3 mg/kg per day) in psoriasis trial revealed increased relative risk (RR) from the general population for all malignancies (RR = 1.6–2.9), skin cancers (RR = 3.8–9.1), and nonmelanoma skin malignancies (RR = 3.8–9.5). Further multivariate analysis noted increased malignancy RR in those patients receiving cyclosporine more than 2 years [38]. However, psoriasis patients' increased overall malignancy (RR = 1.66) and skin cancer (RR = 3.1) RRs compared with the general population confound value of nondisease-matched comparisons [39]. A retrospective, cohort study of 272 inflammatory skin patients treated with cyclosporine over 10 years found no increases in overall malignancy or skin malignancies, although 85% (11 of 13) cancer cases occurred in the 2–4 mg/kg per day group [40]. Similarly retrospective, case–control study of rheumatoid arthritis patients treated with low-dose CsA (2.9 mg/kg per day) for an average of 1.6 years and a large systemic literature review of nearly 1700 psoriasis patients revealed no increase in malignancy rates after accounting for other risk factors [41,42▪]. Taken together, nonmelanoma malignancies such as squamous cell may have a higher incidence in patients on higher (>3 mg/kg per day) and longer term (>2 years) CsA therapy. From limited chronic urticaria trials, larger dermatologic condition trials, and clinical experience increased typical or opportunistic infections rates when using low-dose CsA are not reported. Hypertension, although a fairly common adverse event, is almost always reversible with dosage decreases or discontinuation.

Nephrotoxicity is a primary concern in cyclosporine treatment. Cyclosporine in chronic urticaria studies report increased serum creatinine (>30%) in 0–9% of patients and resolution with decreasing or stopping CsA. Larger psoriasis studies of very low dose cyclosporine (<3 mg/kg per day) for 12–15 months revealed 22–27% of patients with more than 30% increase in serum creatinine [43,44]. However, only 0.5% of patients withdrew due to nephrotoxicity, and 3 months after CsA discontinuation only 3% had a 30–50% increase from baseline [43,44]. Slightly higher cyclosporine doses (<5 mg/kg per day) for 2–3 years in psoriasis patients produced decreased glomerular filtration rates (GFRs) and correlated renal biopsy findings in 25–50% of patients [45,46▪▪]. The GFR decreases and renal biopsy findings in these higher dose CsA patients resolve on stopping CsA; however,

**Table 2. Adverse effects of low-dose calcineurin inhibitors**

| | Adverse effect | Severity | Monitoring |
|---|---|---|---|
| Common (>10%) | Hirsutism/hypertrichosis | Mild | Symptomatic |
| | Headache | Mild to moderate | Symptomatic |
| | Cold/flu symptoms | Mild | Symptomatic |
| | Paresthesias | Mild to moderate | Symptomatic |
| | Nausea and abdominal pain | Mild to moderate | Symptomatic |
| | Nephrotoxicity | Moderate-severe | BUN, creatinine (GFR) |
| | Hypertension | Moderate to severe | Blood pressure |
| Uncommon (5–10%) | Fatigue | Mild | Symptomatic |
| | Weakness | Mild | Symptomatic |
| | Tremor | Mild | Symptomatic |
| | Dizziness | Mild | Symptomatic |
| | Anemia | Mild to Moderate | Complete blood count |
| | Gingival hyperplasia | Mild to moderate | Dental examinations |
| | Hyperuricemia | Mild | Serum uric acid |
| | Arthritis | Mild | Symptomatic |
| | Edema | Mild | Symptomatic |
| Rare (<5%) | Backache/pain | Mild | Symptomatic |
| | Diarrhea | Mild | Symptomatic |
| | Tingling | Mild | Symptomatic |
| | Bilirubinaemia | Mild | Serum AST, ALT, Bilirubin |
| | ↑ Alkaline Phosphatase (ALP) | Mild | Serum ALP |
| | Hyperglycemia | Moderate | Glycosylated Hemoglobin |
| | Hyperlipidemia | Moderate | Fasting lipid panel |
| | Myalgia | Moderate to severe | Symptomatic |
| | Infection | Moderate | Symptomatic |
| | Pruritus | Mild | Symptomatic |

Dosage less than 5mg/kg per day cyclosporine A. Frequency: common (>10%), uncommon (10–5%), rare (<5%). ALT, alanine aminotransferase; AST, aspartate aminotransferase; GFR, glomerular filtration rate.

the results support caution when using dosages greater than 3 mg/kg per day [46▪▪]. In a small number ($n = 20$) of chronic urticaria patients, very low dose cyclosporine (1–2 mg/kg per day) dosage for 5–10 years reported no laboratory abnormalities or increased blood pressures [35▪▪]. Therefore, although monitoring renal function is essential for chronic urticaria patients treated with cyclosporine, the risk of permanent and significant nephrotoxicity appears low and is rare with very low dose (1–2 mg/kg) therapy.

## TACROLIMUS MECHANISM AND STUDIES

Tacrolimus, another immunomodulator from the calcineurin inhibitor class, has been studied for a number of cyclosporine sensitive dermatological conditions such as CIU, atopic dermatitis, and psoriasis [47]. Although tacrolimus has a different molecular target (FK-506 binding protein) than cyclosporine, tacrolimus shares common action through inhibition of calcineurin phosphatase [47]. Similarly to cyclosporine, tacrolimus has been shown *in vitro* to inhibit anti-IgE-mediated mast cell and basophil degranulation along with decreased de-novo prostaglandin $D_2$ synthesis; however, only one small, open-label study [18] has directly tested efficacy in CIU.

Kessel *et al.* [48] conducted a low-dose tacrolimus pilot study in 19 antihistamine refractory CIU patients who required at least intermittent corticosteroids. The 12-week tacrolimus taper provided 0.05–0.07 mg/kg per day for 4 weeks, 0.025–0.035 mg/kg per day for 6 weeks, and 1 mg per day for an additional 2 weeks. Using intention to treat analysis, 12 out of the 19 patients (63%) reported improved symptoms within 5–10 days, improved quality of life, and decreased antihistamine and corticosteroid demand. Due to abdominal pain, diarrhea, and headache, two patients (11%) discontinued tacrolimus treatment. Mild diarrhea ($n = 6$), abdominal pain ($n = 2$), and

tingling of fingers, feet, and lips ($n=2$) were also noted. Of the 10 responders only four reported full relapse at 3 months.

Tacrolimus may offer advantages to cyclosporine in terms of less risk for certain adverse effects such as hirsutism and gingival hyperplasia. Although current data on tacrolimus in chronic urticaria are very limited, it appears to correlate with similar cyclosporine trials. However, further studies are required to improve the level of evidence.

## OVERALL RECOMMENDATIONS

On the basis of limited prospective trials and retrospective data, low-dose cyclosporine ($\leq$3 mg/kg per day) appears to carry the best efficacy to side-effect profile for antihistamine refractory CIU. Before starting therapy, clinicians should ensure vaccinations are up to date and carefully evaluate for contraindications such as uncontrolled hypertension, significant renal disease, serious infections, breast feeding, pregnancy, significant risk of pregnancy, and a previous history of malignancy. Next, we recommend evaluating each patient's chronic medical conditions (hypertension, renal disease, seizures) and current medications for known risk factors associated with cyclosporine adverse drug events as detailed in Table 2 [49]. Blood pressure, blood urea nitrogen, and serum creatinine should be measured at baseline and serially (every 2–4 weeks thereafter) during treatment along with cyclosporine trough levels. Baseline and periodic monitoring of other laboratories should also be considered, including complete blood counts, hepatic function testing, basic electrolyte levels, magnesium levels, glucose, glycosylayed hemoglobin, and lipid levels, as adverse effects have been reported. Therapeutic levels of either cyclosporine or tacrolimus are not required for therapy of chronic urticaria. We find these drug levels useful for considering dosing increases and to monitor for excessive levels, but do not target a specific therapeutic level, as many patients may respond with very low or undetectable trough levels. Baseline and semiannual dental examinations are also recommended in cyclosporine-treated patients due to the risk of gingival hyperplasia.

At least 8 weeks of cyclosporine with dosing adjusted for clinical response and adverse events appears to produce the highest probability of response and lowest relapse rates [22▪▪,24▪▪,26–28,29▪▪,30,31,34▪▪]. Lower doses may not have as rapid a response to treatment. The decision to start with higher doses of calcineurin inhibitors to yield a more rapid clinical response needs to be balanced by the potential for more adverse effects at higher doses. Clinicians must discuss these therapeutic dosing options with patients in order to develop the best individualized therapy. The duration and dose of cyclosporine may be directly correlated with drug-related adverse events favoring the lowest and shortest effective treatment as the optimal regimen. Although remission of chronic urticaria may be achievable in some patients from calcineurin inhibitor therapy, others may require long-term therapy to maintain efficacy.

| | |
|---|---|
| • | What is the efficacy of calcineurin inhibitors in larger populations of CU patients? |
| • | Are calcineurin inhibitors effective in more severe refractory CU patients? |
| • | Are there differences in efficacy or adverse effects between cyclosporine and tacrolimus in CU? |
| • | What is optimal dose and duration of therapy to induce potential remission? |
| • | What is the safety of long term use of calcineurin inhibitors in CU? |
| • | How does the efficacy and potential for remission of calcineurin inhibitors compare to other alternative agents (e.g. omalizumab)? |

**FIGURE 1.** Unresolved questions of calcineurin inhibitors in chronic urticaria.

## FUTURE NEEDS

Although there have been a number of studies on the use of cyclosporine in chronic urticaria, several questions remain unanswered regarding the use of calcineurin inhibitors in chronic urticaria (Fig. 1). Well designed clinical trials with larger sample size of truly antihistamine refractory patients are needed to answer these questions. In the absence of pharmaceutical support for these studies, it will be incumbent on governmental or other agencies to support this much needed research.

## CONCLUSION

Although limited, the available data support the judicious use of low-dose cyclosporine treatment in antihistamine refractory patients, and alternative therapies for these patients have scare, robust evidence. Lower doses of cyclosporine with longer duration likely produce similar clinical efficacy with fewer side-effects. Without large, randomized, blinded placebo controlled trials comparing cyclosporine, omalizumab, dapsone, and similar drugs, uncertainty remains for the optimal treatment of refractory CIU patients. Large comparative trials may appear cost prohibitive; however, relative study costs shrink when considering CIU's estimated $2.5–5 billion direct and indirect costs in the United

States [3▪,50]. In the absence of high-quality data, patients with refractory chronic urticaria nevertheless deserve therapies that have the potential to improve their morbidity and quality of life.

## Acknowledgements

*None.*

## Conflicts of interest

*None declared.*

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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